# Mutant GDF5 enhances ameloblast differentiation via accelerated BMP2-induced Smad1/5/8 phosphorylation

# 論 文 内 容 要 旨

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The development of teeth required reciprocal interactions between mesenchyme and epithelial tissue that modulate cellular proliferation, differentiation and apoptosis. During tooth germ development epithelial tissue thickening is initially occurred to form epithelial placode, and subsequently differentiated into ameloblast that can produce enamel protein such as amelogenin (AMEL), and ameloblastin (AMBN) and enamelin. In addition to basic amelogenesis, ameloblast differentiation also involved in the formation of molar cusps. The transforming growth factors (TGF)-β superfamily including bone morphogenic proteins (BMP) plays an important role in these processes. For instance, BMP-2, 4 and 7, and their type I and II receptors (BMPIA, BMPIIA respectively) have shown to express in dental epithelium. Disruption of BMPIA occurred absent of incisor and molar tooth due to fail to develop past the bud stage of the tooth germ, indicating that the BMPs and their receptors play a critical function during tooth germ development. Growth differentiation factors (GDF), a member of bone morphogenic proteins that has a high affinity to BMPIA and BMPIIA have shown to expressed in cartilage and regulates chondorogenesis, and mutation leads to cause osteoarthritis. In the dental field, GDF-5, 6, 7 have been detected in periodontal ligament and dental follicle, however no report was found in dental germ development.

In the present study, function of GDF-5 in tooth germ development was investigated using ameloblast cell line and mice harboring dominant negative W408R mutation in GDF-5 ($GDF^{W408R}$). Immunohistochemical analysis revealed that GDF-5 and its receptor BMP receptor type IA (BMPRIA) expressed in dental epithelial derived tissue, particular at a stage of enamel formation. By using rat ameloblast cell line SF-2, BMP-2 induced expression of AMEL and AMBN, two ameloblast differentiation maker. In contrast, GDF-5 alone did not induce ameloblast differentiation, however excess amount of GDF-5 interfere the BMP-2 dependent ameloblast differentiation. In addition, $GDF^{W408R}$ showed increasing enamel formation. Over expression of GDF-5 (W408R) in SF-2 cells exhibited enhanced expression of ameloblast marker genes, and induced phosphorylation of SMAD1/5/8, a downstream signaling molecules of BMP. These results indicated that mutant GDF-5 accelerated ameloblast differentiation through the activation of BMP signaling.